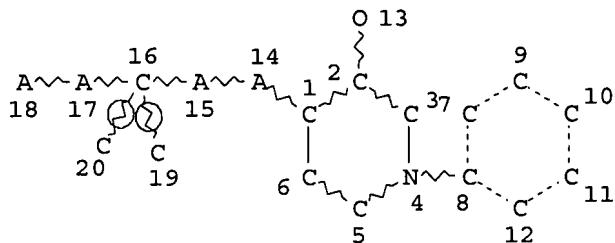


=> d 12  
L2 HAS NO ANSWERS  
L2 STR



NODE ATTRIBUTES:  
DEFAULT MLEVEL IS ATOM  
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:  
RSPEC 3  
NUMBER OF NODES IS 20

STEREO ATTRIBUTES: NONE

=> s 12 ful  
FULL SEARCH INITIATED 09:55:37 FILE 'REGISTRY'  
FULL SCREEN SEARCH COMPLETED - 6262 TO ITERATE

100.0% PROCESSED 6262 ITERATIONS 235 ANSWERS  
SEARCH TIME: 00.00.01

L4 235 SEA SSS FUL L2

=> fil caplus  
COST IN U.S. DOLLARS SINCE FILE TOTAL  
FULL ESTIMATED COST ENTRY SESSION  
173.90 174.11

FILE 'CAPLUS' ENTERED AT 09:55:43 ON 03 OCT 2007  
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.  
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.  
COPYRIGHT (C) 2007 AMERICAN CHEMICAL SOCIETY (ACS)

Copyright of the articles to which records in this database refer is held by the publishers listed in the PUBLISHER (PB) field (available for records published or updated in Chemical Abstracts after December 26, 1996), unless otherwise indicated in the original publications. The CA Lexicon is the copyrighted intellectual property of the American Chemical Society and is provided to assist you in searching databases on STN. Any dissemination, distribution, copying, or storing of this information, without the prior written consent of CAS, is strictly prohibited.

FILE COVERS 1907 - 3 Oct 2007 VOL 147 ISS 15  
FILE LAST UPDATED: 2 Oct 2007 (20071002/ED)

Effective October 17, 2005, revised CAS Information Use Policies apply.  
They are available for your review at:

<http://www.cas.org/infopolicy.html>

=> S 14  
L5 2 L4

=> d bib abs 1-2

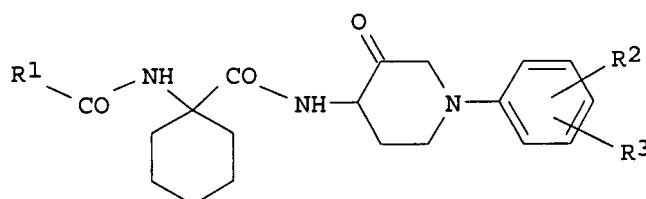
L5 ANSWER 1 OF 2 CAPLUS COPYRIGHT 2007 ACS on STN  
AN 2006:777620 CAPLUS  
DN 145:348526  
TI An orally active cathepsin K inhibitor, furan-2-carboxylic acid, 1-{1-[4-fluoro-2-(2-oxo-pyrrolidin-1-yl)-phenyl]-3-oxo-piperidin-4-ylcarbamoyl}-cyclohexyl-amide (OST-4077), inhibits osteoclast activity in vitro and bone loss in ovariectomized rats  
AU Kim, M. K.; Kim, H. D.; Park, J. H.; Lim, J. I.; Yang, J. S.; Kwak, W. Y.; Sung, S. Y.; Kim, H. J.; Kim, S. H.; Lee, C. H.; Shim, J. Y.; Bae, M. H.; Shin, Y. A.; Huh, Y.; Han, T. D.; Chong, W.; Choi, H.; Ahn, B. N.; Yang, S. O.; Son, M. H.  
CS Dong-A Research Laboratories, Dong-A Pharmaceutical Co., Ltd., Gyeonggi-do, S. Korea  
SO Journal of Pharmacology and Experimental Therapeutics (2006), 318(2), 555-562  
CODEN: JPETAB; ISSN: 0022-3565  
PB American Society for Pharmacology and Experimental Therapeutics  
DT Journal  
LA English  
AB Human cathepsin K, a cysteine proteinase of the papain family, has been recognized as a potential drug target for the treatment of osteoporosis. The predominant expression of cathepsin K in osteoclasts has rendered the enzyme into a major target for the development of novel antiresorptive drugs. Now, we report the pharmacol. properties of OST-4077 [furan-2-carboxylic acid (1-{1-[4-fluoro-2-(2-oxo-pyrrolidin-1-yl)-phenyl]-3-oxo-piperidin-4-ylcarbamoyl}-cyclohexyl)-amide] as a novel selective cathepsin K inhibitor. Human and rat cathepsin K were inhibited in vitro by OST-4077 with the IC<sub>50</sub> values of 11 and 427 nM, resp. OST-4077 suppressed bone resorption induced by rabbit osteoclasts (IC<sub>50</sub>, 37 nM) but did not affect bone mineralization or cellular alkaline phosphatase activity in MC3T3-E1 cells. Parathyroid hormone-induced bone resorption was inhibited in a dose-dependent manner in thyroparathyroidectomized rats gavaged with a single dose of OST-4077 (ED<sub>50</sub>, 69 mg/kg). When given orally twice daily for 4 wk to 3-mo-old ovariectomized (OVX) rats, OST-4077 dose-dependently prevented bone loss, as monitored by bone densitometry, ash content, and urinary excretion of deoxypyridinoline. No change in serum osteocalcin in the OVX rats by OST-4077 suggested that bone formation might not be affected by the agent. In summary, OST-4077 selectively inhibited bone resorbing activities of osteoclasts and prevented bone loss induced by estrogen deficiency but did not affect bone formation. OST-4077, an orally active selective human cathepsin K inhibitor, may have the therapeutic potential for the treatment of diseases characterized by excessive bone loss including osteoporosis.  
RE.CNT 26 THERE ARE 26 CITED REFERENCES AVAILABLE FOR THIS RECORD  
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 2 OF 2 CAPLUS COPYRIGHT 2007 ACS on STN  
AN 2004:101158 CAPLUS  
DN 140:146014  
TI Preparation of 4-[[1-acylaminocyclohexyl]carbonyl]amino]-1-phenylpiperidin-3-ones as cysteine protease inhibitors and processes for their preparation  
IN Lee, Jong-Wook; Lee, Bong-Yong; Lee, Chun-Ho; Hur, Yun; Han, Tae-Dong; Ko, Hyun-Kyoung; Yun, Suk-Won; Shim, Jae-Young; Lim, Joong-In; Son, Moon-Ho; Yang, Jae-Sung; Kim, Mi-Kyung  
PA Yuhan Corporation, S. Korea; Dong-A Pharmaceutical Co., Ltd.  
SO PCT Int. Appl., 158 pp.  
CODEN: PIXXD2  
DT Patent

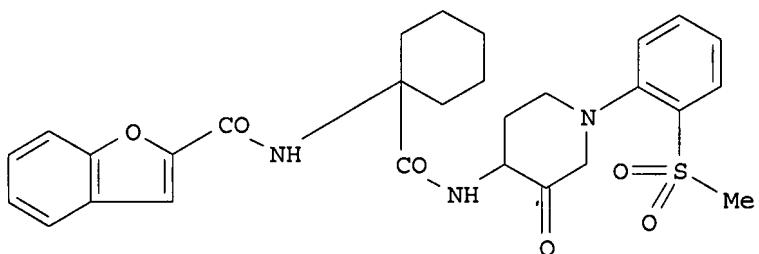
LA English

FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 2004011457	A1	20040205	WO 2003-KR1502	20030726
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
KR 2004010407	A	20040131	KR 2003-51574	20030725
AU 2003281698	A1	20040216	AU 2003-281698	20030726
US 2005234057	A1	20051020	US 2005-521752	20050119
PRAI KR 2002-44164	A	20020726		
KR 2003-13889	A	20030306		
WO 2003-KR1502	W	20030726		
OS MARPAT 140:146014				
GI				



I



II

AB The present invention provides 1-phenylpiperidin-3-ones (shown as I; variables defined below; e.g. II) and pharmaceutically acceptable salts thereof, having cysteine protease inhibitory activity, pharmaceutical compns. containing the same as an active ingredient, and processes for the preparation thereof. For I: R1 is C1-6 alkyl (un)substituted with Ph, C1-6 alkoxy, or benzyloxy; C2-6 alkenyl (un)substituted with phenyl; C3-6 cycloalkyl; C1-5 alkoxy; Ph substituted with halogen, Ph, trifluoromethoxy, oxopyrrolidyl, mono- or di- C1-4 alkylamino or R4-C1-4-alkoxy (R4 is morpholine, pyrrolidine or piperidine); furanyl (un)substituted with  $\geq 1$  functional groups C1-6 alkyl, halogen, and oxopyrrolidyl; benzofuranyl (un)substituted with C1-6 alkyl or R4-C1-4 alkoxy; thiophenyl substituted with C1-6 alkyl or halogen; C1-6 alkylisoxazolyl; pyridyl (un)substituted with halogen; morpholinyl; benzothiophenyl; quinolinyl; pyrazinyl; benzyloxy; oxopyranyl; C1-6 alkyl-7H-imidazo[2,1-b]oxazolyl; C1-6 alkylchromon-2-yl; or (N-tert-butoxycarbonyl)piperidinyl. R2 and R3 are H; hydroxy; nitro; halogen; cyano; C1-6 alkyl (un)substituted with  $\geq 1$  halogen atoms; C1-5 alkoxy; C1-5 alkylthio; furyl; 1H-tetrazol-5-yl; oxazolyl; -C(O)R4;

-S(O)nR6, -NR7R8 (R5 is H; hydroxy; C1-6 alkyl; C1-5 alkoxy; mono- or di-C1-6 alkylamino; or C3-6 cycloalkylamino; R6 is C1-6 alkyl; Ph (un)substituted with C1-4 alkoxy; benzyl (un)substituted with C1-4 alkoxy; R7 and R8 are H; C1-6 alkylcarbonyl (un)substituted with halogen, C1-4 alkoxy, or phenyl; C2-6 alkenylcarbonyl; C1-4 alkoxycarbonyl; C3-6 cycloalkylcarbonyl; benzoyl (un)substituted with  $\geq 1$  halogen atoms; mono- or di- C1-4 alkylcarbamoyl; or C1-4 alkylsulfonyl, or bonded each ether to form a morpholine, azetidin-2-one, 3,3-dimethylazetidin-2-one, pyrrolidin-2-one, pyrrole, 2,5-dihydropyrrole, piperidin-2-one, oxazolidin-2-one, imidazolidin-2-one, imidazolidin-2,5-dione, tetrazole, 1,1-dioxoisothiazolidine, or C1-6 alkylaziridin-2-one ring; and n = 0-2). Methods of preparation are claimed and .apprx.190 example preps. are included. For example, II was prepared in 4 steps starting with amide formation from tert-Bu 4-amino-3-hydroxypiperidine-1-carboxylate and 1-[N-[(benzofuran-2-yl)carbonyl]amino]cyclohexanecarboxylic acid to give 4-[N-[[1-[N-[(benzofuran-2-yl)carbonyl]amino]cyclohexyl]carbonyl]amino]-1-(tert-butoxycarbonyl)-3-piperidinol followed by N-deprotection to give 4-[N-[[1-[N-[(benzofuran-2-yl)carbonyl]amino]cyclohexyl]carbonyl]amino]-3-piperidinol hydrochloride, followed by N-arylation with 2-fluorophenyl Me sulfone in the presence of K<sub>2</sub>CO<sub>3</sub> to give 4-[N-[[1-[N-[(benzofuran-2-yl)carbonyl]amino]cyclohexyl]carbonyl]amino]-1-(2-methylsulfonylphenyl)piperidin-3-ol, followed by oxidation by pyridine-SO<sub>3</sub> complex to give II. In some other N-arylations, in addition to the presence of a base, a Pd complex was used as catalyst. IC<sub>50</sub> values for inhibition of cathepsin K activity and selectivity for cathepsin K vs. other cathepsins (C, G, H, L, S) are tabulated for many examples of I; e.g. 8.17 nM for II for cathepsin K (382, >240, >240, 138, and 133 nM, resp., for others). The bioavailabilities of I by oral administrations, which were calculated after i.v. administrations of 10 mg/kg of rat, were .apprx.30-90 %.

RE.CNT 4        THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD  
ALL CITATIONS AVAILABLE IN THE RE FORMAT